Available online at www.sciencedirect.com

ScienceDirect

Procedia Chemistry 19 (2016) 153 – 161

Procedia Chemistry

5th International Conference on Recent Advances in Materials, Minerals and Environment (RAMM) & 2nd International Postgraduate Conference on Materials, Mineral and Polymer (MAMIP), 4-6 August 2015

Mass transport analysis in linear microdialysis probes utilizing structural characterization technique

Kho Chun Min[a], Zainal Arifin Ahmad[a], Siti Kartini Enche Ab Rahim[b], Norazharuddin Shah Abdullah[a]

[a]*Structural Materials Niche Area, School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia, Engineering Campus, 14300 Nibong Tebal, Penang, Malaysia.*
[b]*Department of Chemical Engineering Technology, Faculty of Engineering Technology,Universiti Malaysia Perlis, Level 1, Block S2, Uniciti Alam Campus, 02100 Sungai Chuchuh, Padang Besar, Perlis, Malaysia.*

Abstract

Microdialysis is a separation technique widely used for sampling and monitoring purposes. Microdialysis requires a (microdialysis) probe to be inserted to the designated area of study. Separation procedure is completed by using a selective semi-permeable membrane attached to the microdialysis proe. Despite being a well-established technique, there are still issues regarding the performance of the microdialysis probe. The biggest issue is arguably that the concentration of solutes collected via microdialysis sampling represents only 20-30% of the original concentration from the sampling site. This issue can be resolved by understanding mass transport phenomena within the microdialysis probe and its surroundings. One straightforward, yet sustainable way to analyze mass transport is through the use of computational modelling. In this paper, a mathematical framework, representing glucose recovery from a quiescent media using a microdialysis probe of linear design was described. Governing equations, boundary conditions and operational parameters were justifiably selected. Different diffusion coefficients were used to describe the mass transport through the quiescent media, semi-permeable membrane and the probe‘s lumen. Subsequently, the influence of some identified parameters, on the overall recovery is examined. Scanning electron microscopy imaging was used to study the physical characteristics of the microdialysis membrane, thus being utilized to estimate the

Peer-review under responsibility of School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia

Keywords: microdialysis; mathematical modelling; diffusion coefficient

* Corresponding author. Tel.: +604-599 5261.
E-mail address: azhar.abdullah@usm.my

Peer-review under responsibility of School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia
doi:10.1016/j.proche.2016.03.017

diffusion coefficient values. The impact of using different diffusion coefficient values on the overall recovery was also discussed.

Peer-review under responsibility of School of Materials and Mineral Resources Engineering, Universiti Sains Malaysia

Nomenclature

c	concentration of solute collected from microdialysis sampling (mol m^{-3})
c_g	concentration of glucose at sampling site (mol m^{-3})
c_o	concentration of solute at microdialysis probe inlet (mol m^{-3})
c_s	concentration of solute at sampling site (mol m^{-3})
D	diffusion coefficient / diffusivity (m^2 s^{-1})
D_{AB}	molecular diffusion of a solute A in medium B (m^2 s^{-1})
D_g	diffusivity of glucose in water (m^2 s^{-1})
D_m	D_{AB} as hindered by the semi-permeable membrane (m^2 s^{-1})
ECF	extracellular fluid
F	external forces acting on fluid
l_m	length of semipermeable membrane (m)
MWCO	molecular weight cut off
NS	Navier-Stokes
PI	probe interior
PSA	probe surrounding area
R	inner radius of microdialysis probe (m)
R_p	average radius of glucose molecule (m)
R_s	radius of pore at the surface of membrane (m)
RR	relative recovery
u	fluid velocity (m s^{-1})
u_{ns}	fluid velocity in radial (horizontal) direction (m s^{-1})
V	flow rate of perfuse solution in microdialysis probe (L min^{-1})
v_o	velocity of perfuse solution in microdialysis probe (m s^{-1})
v_{ns}	fluid velocity in axial (vertical) direction (m s^{-1})
α	hindrance factor of membrane
i_m	thickness of semipermeable membrane (m)
i_c	thickness of connecting pipes' wall (m)
ε_p	porosity of membrane (%)
η	dynamic viscosity of perfuse solution (kg m^{-1} s^{-1})
$\xi_{d,i}$	hindrance factor for diffusion
ρ	density of perfuse solution (kg m^{-3})
τ	tortuosity of membrane

1. Introduction

1.1. Introduction

Microdialysis is a membrane based separation technique introduced in the 1970's. This technique is most commonly used for sampling neurotransmitters as well as other diffusible solutes from extracellular space in tissues for pharmacokinetic and neuropharmacological studies[1]. When used for in vivo studies, a probe (commonly known as microdialysis probe) will be inserted into the tissue area of the specimen. With respect to this, microdialysis is considered to be a minimally invasive technique. Microdialysis applications are not limited to in vivo studies. Various researchers have reported using microdialysis technique for in vitro studies as well[1-3]. Apart

from sampling, microdialysis is also widely praised by researchers as a continuous monitoring tool for both living and anaesthetized specimens.

Microdialysis technique utilizes a semipermeable membrane to selectively collect the solute of interest from the sampling site. The selectivity of the sampling substance is often based on the pore size of the membrane, which is more commonly known as molecular weight cut off (MWCO). In general, MWCO is defined as the lowest molecular weight (in Daltons, Da) at which greater than 90% of a solute with a known molecular weight is retained by the membrane. In other words, the semipermeable membrane will allow 90% of smaller solutes to pass through it, while larger substances are rejected, hence the selection process. Apart of having relatively consistence pore size throughout the membrane, the membrane itself has to be chemically inert so that the collected substance can accurately reflect the actual concentration from the sampling site.

Till date, there are number of composite filtration membranes which are commercially used in membrane separation processes, with cellulose acetate (CA), polyamide (PA), polyacrylonitrile (PAN), polyethersulfone (PES), and polysulfonate (PS) being the more common ones[4]. A study conducted by Metha and Zydney[5] shows that using different materials for the semipermeable membrane will only have minimal impact on the separations process and the main factor that determines the selectivity of the membrane is still the MWCO of the membrane.

For most microdialysis applications, the concentration of the solute collected from the microdialysis sampling will only represent a portion of the actual concentration of the sampling site. Further calibration procedures are required to accurately determine the concentration of the sampling site. However, at present, most calibration procedures involves (1) costly and time-consuming repetitions of microdialysis sampling to obtain accurate data, (2) extremely sensitive analytical equipment to detect the concentration of the solute, and (3) handling of samples with extremely small volume, which can be rather cumbersome[6]. In order to address these issues, studies regarding limitations of mass transport through the semipermeable membrane such as those described by Yang et al.[7] and Abdullah et al.[8] are required.

One straightforward yet sustainable method to study the mass transport in microdialysis application is through computational modeling. A mathematical model is usually constructed based on combination of computational simulations and experimental results[9]. Although mathematical models are less likely to be used to predict the outcome of experimental procedures, these models serves as an important tool to study the mechanism behind the experimental procedures. Implementing modeling work in microdialysis application will help researchers understand the mass transport mechanism that limits the solute movement through the membrane, which serves as the stepping stone to improve the extraction efficiency (also known as relative recovery) of microdialysis applications for in vivo studies. In addition, mathematical model allows the solute‘s concentration of the probe surrounding area to be projected, something which is unlikely achieved experimentally.

In order to create a robust and accurate mathematical model, all related operation and design parameters must first be defined. This paper aims to serve as an initial effort to create a fitting mathematical model for a linear designed microdialysis probe equipped with PAN membrane. Several physical properties that are required in the mathematical equations for modeling purpose shall be determined using physical characterization techniques, such as scanning electron microscopy.

1.2. Theoretical background

It is generally accepted that the mass transport mechanism in microdialysis applications is driven by concentration gradient of solute in the microdialysis probe and the probe surrounding area. As such, various researchers have concluded that the solute passage from the probe surrounding area through the semi-permeable membrane, and finally into the microdialysis probe in a diffusion limited system[6]. In this paper, the diffusion is represented by Fick‘s first law of diffusion, as shown in Eqn. 1[10].

$$J = -D\frac{\partial c}{\partial x} \tag{1}$$

In the equation above, J is the diffusional flux ($mol.m^{-2}.s^{-1}$), D is the diffusion coefficient ($m^2.s^{-1}$), c is the concentration ($mol.m^{-3}$) and x is the length which diffusion occur (m). The negative sign indicates that the solute

will diffuse from a more concentrated to a less concentrated medium[10,11]. The following definitions are made while applying this law: 1) there is no solute-solute chemical reactions occur, and 2) the diffusion coefficient is independent of temperature and pressure changes. These assumptions are based on the conditions that this model only contains one solute in one medium, and conducted at a controlled environment (i.e. at room temperature and pressure). For microdialysis applications, the concentration gradient and the length are both operational parameters, which can be explicitly defined through experimental procedures. However, defining the molecular diffusion coefficient for microdialysis applications required further consideration as it involves fluid flow through semipermeable membrane.

Diffusion coefficient (D) is typically defined as the rate at which a substance is transported over opposite sides of a unit cube of a system due to the existence of a concentration gradient[10,11]. Diffusion coefficient of a solute molecule in a fluid medium is also commonly known as molecular diffusivity and is expressed in the form of D_{AB}, in which A is the diffusion species while B is the medium. In microdialysis applications, D is required for the probe surrounding area (PSA), the semipermeable membrane and the microdialysis probe's interior (PI), with each subdomain having a different D value, as illustrated in later part of this paper (Fig.1). The D for PSA and PI are defined in the form of unhindered diffusion, or molecular diffusion which can be determined through experimental works[11]. However, the D for the semi-permeable membrane is considered to be hindered by the porous structure of the membrane. Further derivation is required to define D for membrane (or simply, D_m).

Throughout the years, a number of D_m values have been derived by various researchers, as listed in Table 1. Till date, not much work has been done in comparing the effect of using different diffusion coefficient in modeling work. This paper will discuss the effect of using different D_m on the recovery of mathematical model designed based on a linear microdialysis probe. All D_m listed below are constructed with the assumption that the membrane is homogeneous and D_m represents the average membrane diffusivity at any point of the membrane.

Table 1: List of commonly used diffusion coefficient for modeling mass transport through porous membrane.

Model no.	Diffusion coefficient equation		References
I	$\frac{D_m}{D_{AB}} = \left(1-\frac{R_s}{R_p}\right)^2 \left(1 - 2.10\frac{R_s}{R_p} + 2.09\frac{R_s^3}{R_p^3} - 0.95\frac{R_s^5}{R_p^5}\right)$	(2)	12
II	$D_m = D_{AB}\frac{\varepsilon_p}{\tau^2}$	(3)	13
III	$D_m = D_{AB}\frac{\varepsilon_p}{\tau}\xi_{d,i}$	(4)	10,14
IV	$D_m = \frac{D_{AB}}{\alpha}$	(5)	8,15

2. Methodology

2.1. PAN membrane characterization

PAN membrane from a commercial linear microdialysis probe (1cm, 30 kDa MWCO) was characterized by using extreme high resolution field emission scanning electron microscope (XHR-FESEM), FEI Verios 460L model. Prior to the characterization, the membrane was soaked in distilled water overnight to remove the glycerol coating on the membrane[3]. The PAN membrane was later dried at room temperature and cryogenically fractured using liquid nitrogen. The cross-section area of the membrane is also analysed using XHR-FESEM.

2.2. Formulation for modelling work

The modelling work for this paper was accomplished using Comsol Multiphysics 3.5a. The domain was plotted in axial symmetry, with subdomains comprises of PI, the membrane area, and PSA, as shown in Fig. 1. Insulated boundaries are used to describe the connecting pipes attached to the microdialysis probe. The domain of the modelling space was extended to a point that the original concentration of the sampled substance in PAS was not

be affected by the insertion of the microdialysis probe.

The modelling work was based on in vitro sampling of glucose in a quiescent media with known glucose concentration. From literature, the mass transport in PSA and through the semipermeable membrane was defined to be diffusion limited[6,11]. During microdialysis sampling, a perfused solution is consistently flushed through the microdialysis probe in axial direction of the probe. The PI subdomain involves motion of fluid flow. Simplified Navier-Stokes equations (NS) for incompressible fluid were nominated in this case to describe the fluid flow[12]. In addition, the mass transfer in this subdomain is both diffusive and convective, due to the occurrence of concentration gradient and fluid flow. The detailed equations, as well as the boundary conditions used for this modelling are described in Table 2, while the physical and operational parameters used for this model are listed in Table 3. All fluids involved in this model are defined as incompressible Newtonian fluid.

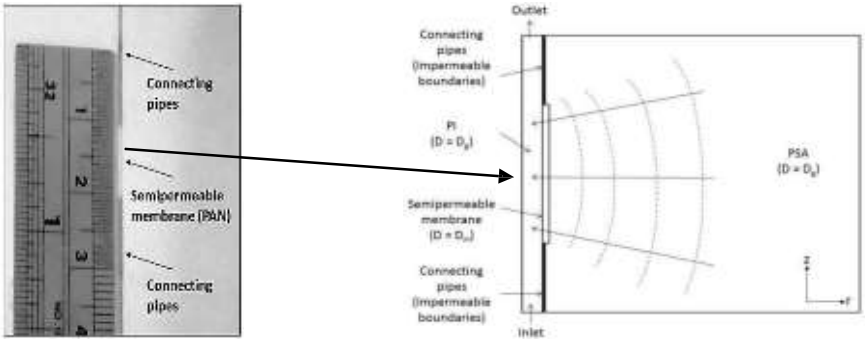


Fig. 1: Illustrated subdomain geometries for linear designed microdialysis probe using Comsol. In the image, z represents axial (vertical) direction while r represents radial (horizontal) direction.

Table 2: Governing equations and boundary conditions for each subdomain.

Subdomain	Transport equation		Boundary conditions
PI	NS and continuity equation for incompressible fluid :		
	$\rho(u\cdot\nabla)u = \nabla\cdot\left[-pI+\eta\left((\nabla u+(\nabla u)^T)\right)\right]+F$	(6a)	u = 0 at membrane wall and connecting pipes' wall
	$\nabla\cdot u = 0$	(6b)	$v_{ns} = v_o$, $u_{ns} = 0$ at inlet
	Diffusion-convection equation:		
	$\nabla\cdot(-D_g\nabla c) = -u\cdot c$	(7)	$c = c_o$ at inlet
			$\frac{\partial c}{\partial r} = 0$ at asymmetrical and insulated boundary
			$D_g\frac{\partial c}{\partial r} = D_m\frac{\partial c}{\partial r}$ at membrane-PI boundary
Membrane	Diffusion equation:		
	$\nabla\cdot(-D_m\nabla c) = 0$	(8)	$D_g\frac{\partial c}{\partial r} = D_m\frac{\partial c}{\partial r}$ at membrane-PI boundary
			$D_m\frac{\partial c}{\partial r} = D_g\frac{\partial c}{\partial r}$ at membrane-PSA boundary
PSA	Diffusion equation:		
	$\nabla\cdot(-D_g\nabla c) = 0$	(9)	$D_m\frac{\partial c}{\partial r} = D_g\frac{\partial c}{\partial r}$ at membrane-PSA boundary
			$c = c_g$ at PSA boundaries

Table 3: Operating and design parameter values used for this modelling work.

Model parameter	Symbol	Unit	Value	References
Inner radius of microdialysis probe	R	M	9.0×10^{-5}	-
Thickness of semipermeable membrane	i_m	M	3.0×10^{-5}	-
Thickness of connecting pipes' wall	i_c	M	2.0×10^{-5}	-
Length of semipermeable membrane	l_m	M	1.0×10^{-2}	-

Flow rate of perfuse solution in microdialysis probe	V	$L\ min^{-1}$	1.00×10^{-6}	1
Velocity of perfuse solution in microdialysis probe	v_o	$m\ s^{-1}$	6.55×10^{-4}	-
Concentration of glucose at microdialysis probe inlet	c_o	$mol\ m^{-3}$	0	-
Density of perfuse solution	ρ	$kg\ m^{-3}$	993.37	8,15
Dynamic viscosity of perfuse solution	η	$kg\ m^{-1}\ s^{-1}$	0.000692	8,15
Diffusivity of glucose in water	D_g	$m^2\ s^{-1}$	5.4×10^{-10}	8,15
Concentration of glucose at sampling site	c_g	$mol\ m^{-3}$	5.55	8,15
Radius of glucose molecule (average)	R_p	M	$1.5\times\times10^{-9}$	16
Porosity of membrane	ε_p	%	15	17
Tortuosity of membrane	τ	-	1.5	18,19
Radius of pore at the surface of membrane	R_s	M	1.5×10^{-8}	17
Hindrance factor for diffusion	$\xi_{d,i}$	-	0.78	10
Hindrance factor of membrane	α	-	10	8,15

3. Results and discussion

3.1. SEM imaging of PAN membrane

SEM images of the 30kDa PAN membrane used for microdialysis application are shown in Fig.2.

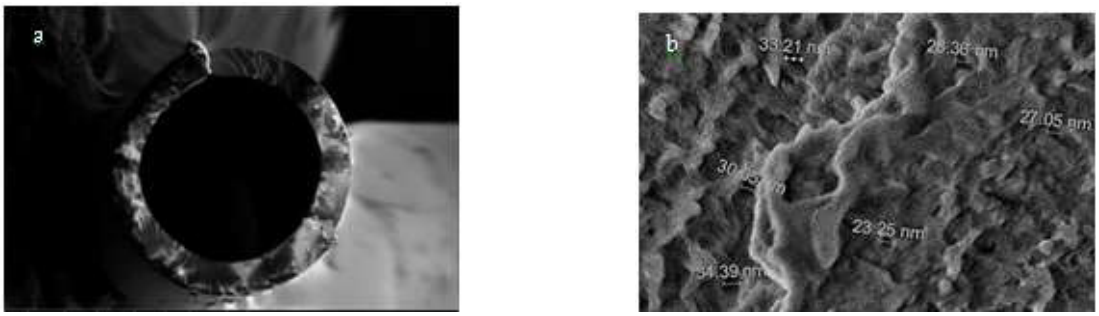


Fig. 2: a) SEM micrograph of the cross-section of PAN membrane at 500× magnifications. b) SEM micrograph of the surface of PAN membrane at 431k magnifications.

Based on Fig. 2a, the inner diameter of the hollow membrane was approximately 180 µm while the membrane thickness is in the range of 30 µm, the obtained values are similar to what was provided by supplier. From Fig.2b the diameter of the pore size for PAN membrane was in the range of 15-40 nm. Similar results were also reported by Clark and Lucas[14]. For modelling purpose, an average pore size with radius of 15 nm was used, with an estimated porosity of 15% of the surface area. This result is based on atomic force microscopy (AFM) analysis on the same membrane in literature[14].

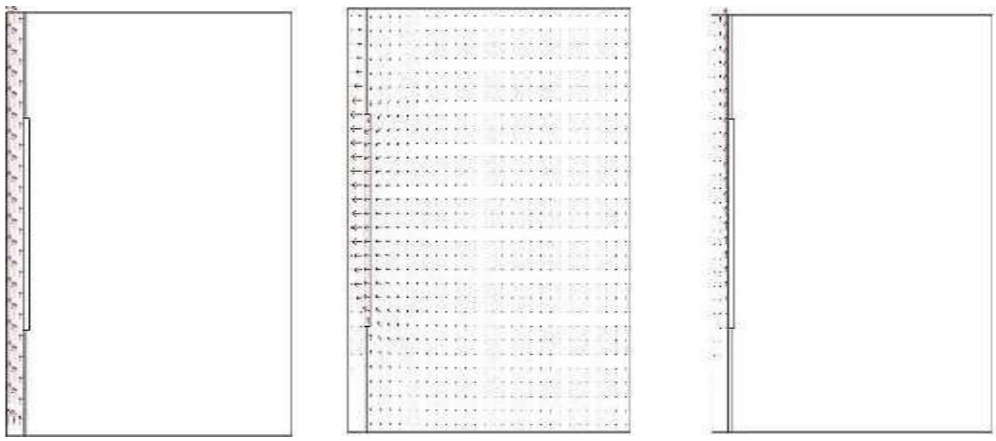
3.2. Outcome of modeling work

The fluid flow around the membrane area for this modeling work is presented in Fig. 3. The velocity profile for the PI subdomain is highest at the asymmetrical boundary while there is no flow at both the membrane and insulated boundary. Also, the velocity profile only occurs in the PI subdomain, while the membrane area and PSA was not affected by the inlet velocity. However, the inlet velocity does affect the convective flux, which only occurs in the PI subdomain. Diffusive flux occurs in all three subdomains, with a relatively large area of the PSA around the membrane area affected. For this model, it is assumed that the glucose concentration in PSA is relatively abundant so that the glucose concentration does not deplete during the sampling process.

Apart from mass transport profile, another important aspect in microdialysis sampling is the efficiency of the sampling process. The efficiency of microdialysis sampling is often expressed in the form of relative recovery (RR), which can be expressed by the following equation (10)[1,6]:

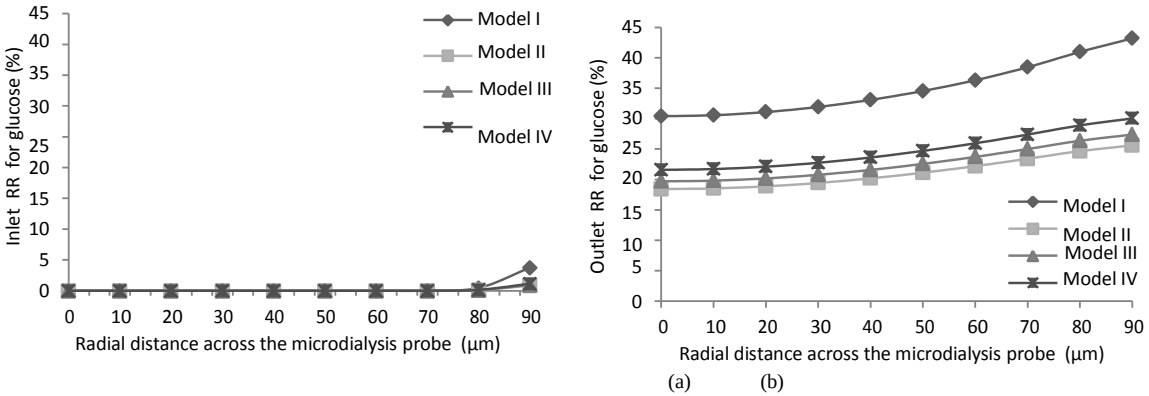
$$RR = \left(\frac{c - c_o}{c_s} \right) \times 100\% \quad (10)$$

where c is the concentration of solute collected, c_o is the concentration of the solute in inlet velocity and c_s is the concentration of the solute at the sampling site. However, unlike experimental work, the concentration profiles for the mathematical modeling must first be analyzed before the RR can be determined. For this modeling work, the glucose concentration fraction as the fluid enters and exit the microdialysis probe, based on the different diffusion coefficient (as describe earlier) was examined. The results are plotted into a graph as shown in Fig. 4.



(a) (b) (c)

Fig. 3: (a) velocity profile around the membrane area which caused by inlet velocity based on NS equations, (b) diffusive flux of glucose from PSA to PI, and (c) convective flux of glucose concentration in PI.



(a) (b)

Fig. 4: Glucose concentration fraction recovered from the microdialysis probe over radial distance across the microdialysis probe at (a) inlet of the microdialysis probe, and (b) the outlet of microdialysis probe.

Figure 4 shows that at the membrane outlet of the microdialysis probe, glucose was transported through the microdialysis probe in a slightly different manner for one of the four D_m approximations (i.e., Model I) in this modelling work. Each D_m approximations displayed a similar RR value at the inlet of the microdialysis membrane, which was approximately 0.19%. At the membrane outlet of the microdialysis probe, all four models showed different RR values, with an average of: 34.87% for Model I, 21.23% for Model II, 22.69% for Model III and

24.84% for Model IV. Model I shows significantly higher RR value compared to others. This is presumably due to the fact that Model II, III and IV included more detailed membrane parameters such as porosity and tortuosity while Model I solely depends on the pore size of the membrane and size of the diffusing molecule. For our case, glucose molecule with an average radius of 1 nm was used as the diffusing molecule. Thus, it can be concluded that membrane parameters such as porosity and tortuosity may as well influence (theoretically) the solute diffusivity within the probe membrane, which would eventually affect the overall performance of the microdialysis probe.

4. Conclusion

In this paper, a mathematical framework for a linear design microdialysis probe was put together. The governing equations and boundary conditions for each subdomain were carefully defined. Some of the common design and operational parameters for microdialysis sampling is obtained from literature to support the mathematical model. The different diffusion coefficient values of the membrane attached to the microdialysis as proposed by various researchers are compared. It can be conclude that membrane factors such as pore size, porosity and tortuosity of the membrane should be considered while deriving an accurate equation for the diffusion coefficient of the microdialysis membrane at inlet and outlet region.

It is proven that mathematical modeling offers a feasible yet effective route to study theoretical mass transport inside the microdialysis probe. Such results can be rather laborious if it were to obtain through experimental work, due to the small size of microdialysis probe. Understanding mass transport allows researchers to design more effective probes for microdialysis applications. Nevertheless, it should be noted that modeling work alone would not be sufficient to be used to predict the outcome of sampling process. Instead, mathematical modeling can be used as a constructive tool to complement the studies of microdialysis applications. Supports from experimental works and characterization works are essential in order to build robust and accurate mathematical models. As such, future work will focus on comparing mathematical results to experimental result with both using the same operational parameters.

Acknowledgements

The authors would like to express their gratitude to Universiti Sains Malaysia (USM) for financial support, through the Research University Individual (RUI) grant (RUI1001/PBAHAN/814177). The Ministry of Higher Education (MOHE), Malaysia is also appreciated for funding the research project (through MyPhD). The authors would also like to thank Mr. Mohd Zharif Ahmad Thimizir for his technical support in FESEM analysis.

References

1. Song Y, Lunte CE. Comparison of calibration by delivery versus no net flux for quantitative in vivo microdialysis sampling. *Anal Chim Acta* 1999;**379**:251-62.
2. Schutte RJ, Oshodi SA, Reichert WM. In vitro characterization of microdialysis sampling of macromolecules. *Anal Chem* 2004;**76**:6058-63.
3. Jacobson I, Sandberg M, Hamberger A. Mass transfer in brain dialysis devices — a new method for the estimation of extracellular amino acids concentration. *J Neurosci Methods* 1985;**15**:263-8.
4. Ramakrishna S, Ma Z, Matsuura T. *Polymer Membranes in Biotechnology: Preparation, Functionalization and Application*: Imperial College Press; 2011.
5. Mehta A, Zydney AL. Permeability and selectivity analysis for ultrafiltration membranes. *J Membr Sci* 2005;**249**:245-9.
6. Kho CM, Aziz A, Ahmad ZA, Enche Ab Rahim SK, Abdullah NS. Initial efforts in modelling mass transport in microdialysis probes: physical characterization of the microdialysis probe membrane. *Adv Mater Res* 2015;**1087**:365-369.
7. Yang H, Peters JL, Allen C, Chern SS, Coalson RD, Michael AC. A theoretical description of microdialysis with mass transport coupled to chemical events. *Anal Chem* 2000;**72**:2042-49.
8. Abdullah NS, Jones DR, Das DB. Nutrient transport in bioreactors for bone tissue growth: Why do hollow fibre membrane bioreactors work? *Chem Eng Sci* 2009;**64**:109-25.
9. Chuzlov VA, Chekantsev NV, Ivanchina ED. Development of complex mathematical model of light naphtha isomerization and

rectification processes. *Procedia Chem* 2014;**10**:236-43.
10. Nagy E. *Basic equations of the mass transport through a membrane layer*: Elsevier; 2012.
11. Cussler EL. *Diffusion: Mass Transfer in Fluid Systems*: Cambridge University Press; 2009.
12. Renkin EM. Filtration, diffusion, and molecular sieving through porous cellulose membranes. *J Gen Physiol* 1954;**38**:225-43.
13. Van Brakel J, Heertjes PM. Analysis of diffusion in macroporous media in terms of a porosity, a tortuosity and a constrictivity factor. *Int J Heat Mass Transfer* 1974;**17**:1093-103.
14. Deen WM. Hindered transport of large molecules in liquid-filled pores. *AIChE J* 1987;**33**:1409-25.
15. Ye H, Das DB, Triffitt JT, Cui Z. Modelling nutrient transport in hollow fibre membrane bioreactors for growing three-dimensional bone tissue. *J Membr Sci* 2006;**272**:169-78.
16. Minoli D. *Nanotechnology Applications to Telecommunications and Networking*: Wiley; 2005.
17. Clark MM, Lucas P. Diffusion and partitioning of humic acid in a porous ultrafiltration membrane. *J Membr Sci* 1998;**143**:13-25
18. Mott HV, Weber WJ. Factors influencing organic contaminant diffusivities in soil-bentonite cutoff barriers. *Environ Sci Technol* 1991;**25**:1708-15
19. Shen L, Chen Z. Critical review of the impact of tortuosity on diffusion. *Chem Eng Sci* 2007;**62**:3748-55.